

# Finding the basic neighborhood in variable range Markov random fields: application in SNP association studies

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## Abstract

The SNPs (Single Nucleotide Polymorphisms) genotyping platforms are of great value for gene mapping of complex diseases. Nowadays, the high-density of these molecular markers enables studies of dependence patterns between loci over the genome, allowing a simultaneous inference of dependence structure and disease association. In this paper we propose a method based on the theory of variable range Markov random fields to estimate the extent of dependence among SNPs allowing variable windows along the genome. The advantage of this method is that it allows the simultaneous prediction of dependence and independence regions among SNPs, without restricting *a priori* the range of dependence. We introduce an estimator based on the idea of penalized maximum likelihood to find the conditional dependence neighborhood of each SNP in the sample and we prove its consistency. We apply our method to autosomal SNPs genotypic data with unknown phase in the context of case-control association studies. By examining rheumatoid arthritis data from the *Genetic Analysis Workshop 16* (GAW16), we show the utility of the Markov model under variable range dependence.

# 1 Introduction

Genome-wide genetic mapping studies based on linkage disequilibrium (LD) have been encouraged from the availability of high-density SNPs (Single Nucleotide Polymorphisms) genotyping platforms. Since the individual SNP effect is expected to be small, a challenge has been to find blocks of SNPs with effect on diseases. This problem requires the consideration of a model of the dependence structure among loci over the genome, see for example Akey et al. (2001); Greenspan and Geiger (2006); Browning (2006); Kim et al. (2008).

In this paper we propose a method based on the theory of variable range Markov random fields to estimate the extent of dependence among SNPs allowing variable windows along the genome. In order to infer the range of dependence for each SNP, we propose a criterion based on penalized maximum likelihood. The main theoretical contribution of this paper is the proof of the consistency of this estimator, as the sample size diverges.

As a consequence of our model, we show how the dependence information inferred can be used to construct independent blocks of SNPs that can be associated with a response variable in the context of case-control studies. Tools such as the Chi-square statistic are adopted to study the association of each block and the response variable. The main advantage of this method is that it allows, without restriction of range, the simultaneous prediction of dependence and independence regions among SNPs.

Methods based on penalized maximum likelihood to infer the range of dependence of Markov random fields have been proposed in the literature before, see for example Csiszár and Talata (2006a); Löcherbach and Orlandi (2011). The main difference between these approaches and our is that these methods assume a fixed (and symmetric) neighborhood for each variable, because they based the inference procedure on only one sample of the process. In our context, we have at hand several independent realizations of the process, corresponding to different individuals in the sample, and this allows us to assume an inhomogeneous process with different neighborhoods for each variable.

In order to illustrate the potential of our method to infer variable dependence struc-

tures and disease association we will consider rheumatoid arthritis data from the GAW16. Although our methodology is driven to SNP genotypic sequence, extension for allele sequences is also possible.

The paper is organized as follows. In Section 2 we define the variable range Markov random field, introduce the criterion to estimate the range of dependence for each variable and state the consistency result. In Section 3 we show how to apply our method to infer the dependence structure in SNPs maps and to study association with a response variable in a case-control study. Finally, in Section 4 we prove the main theoretical result of this paper.

## 2 Variable range Markov random fields

Let  $A$  denote a finite alphabet and let  $\mathbb{P}$  be a probability distribution over  $A^{\mathbb{Z}}$ , equipped with the usual  $\sigma$ -algebra generated by the cylinder sets. Given an element  $i \in \mathbb{Z}$ , called a *site*, we will denote by  $X_i$  the marginal random variable obtained by the canonical projection of elements in  $A^{\mathbb{Z}}$ . Given two non-negative integers  $l$  and  $r$ , we will denote by  $\Delta_{l,r}^i$  the union of the two integer intervals to the left and to the right of site  $i$  of length  $l$  and  $r$ , respectively; that is  $\Delta_{l,r}^i = \{i-l, \dots, i-1, i+1, i+r\}$ . We will also denote by  $X_{\Delta_{l,r}^i}$  the random vector  $\{X_j : j \in \Delta_{l,r}^i\}$  and similarly  $x_{\Delta_{l,r}^i}$  will denote an element of  $A^{\Delta_{l,r}^i}$ .

We say  $\mathbb{P}$  is a *variable range* Markov random field on  $A$  if for any  $i \in \mathbb{Z}$  there exist two integers  $l_i$  and  $r_i$  such that for all  $L \geq l_i$  and all  $R \geq r_i$  we have

$$\mathbb{P}(X_i = x_i \mid X_k = x_k, k \in \Delta_{L,R}^i) = \mathbb{P}(X_j = x_j \mid X_k = x_k, k \in \Delta_{l_i,r_i}^i), \quad (1)$$

for all  $x_i \in A$  and all  $x_{\Delta_{L,R}^i}$  for which  $\mathbb{P}(X_{\Delta_{L,R}^i} = x_{\Delta_{L,R}^i}) > 0$ .

Observe that the size of the neighborhood  $\Delta_{l_i,r_i}^i$  may depend on the specific site  $i$ , for that reason we call our model a variable range Markov random field.

*Remark 2.1.* If  $(l_i, r_i)$  satisfies equation (1) then any pair  $(l, r)$  with  $l \geq l_i$  and  $r \geq r_i$  will also satisfy equation (1). For this reason in the sequel we assume  $l_i$  and  $r_i$  are the minimal

integers satisfying (1), calling the set  $\Delta_{l_i, r_i}^i$  the *basic neighborhood* of site  $i$ .

*Remark 2.2.* Note that if  $X_i$  and  $X_j$  are not conditionally independent given all the remaining variables then  $[i; j] \subset \Delta_{l_i, r_i}^i \cap \Delta_{l_j, r_j}^j$ , where  $[i; j]$  denotes the integer interval  $\{i, i+1, \dots, j-1, j\}$ . On the other hand, if there exists  $\ell$  such that  $r_i \leq \ell - i$  for any  $i \leq \ell$  and  $l_j \leq j - \ell$  for any  $j > \ell$ , then  $X_i$  is independent of  $X_j$  for any  $i \leq \ell$  and any  $j > \ell$ .

In what follows we will focus on the problem of identifying the basic neighborhood of a given site  $i \in \mathbb{Z}$ . Without loss of generality we will take  $i = 0$  and we will simply write  $\Delta_{l_0, r_0}^0 = \Delta_{l_0, r_0}$ . We will assume we have an independent sample of size  $n$  of  $(X_{-L_0}, \dots, X_0, \dots, X_{R_0})$ , with  $L_0 \geq l_0$  and  $R_0 \geq r_0$ . We will denote by  $x_j^{(i)}$  the value taken by the  $j$ -th variable in the  $i$ -th observation. Our goal is to estimate the basic neighborhood  $\Delta_{l_0, r_0}$  (by estimating the parameters  $l_0$  and  $r_0$ ) and the conditional probabilities given by (1), based on this sample.

Given two sequences  $w = (w_{-l}, \dots, w_{-1}) \in A^l$  and  $v = (v_1, \dots, v_r) \in A^r$  and a symbol  $a \in A$  we will denote by  $p(a|w, v)$  and  $p(w, a, v)$  the conditional (respectively joint) probability given by

$$p(a|w, v) = \mathbb{P}(X_0 = a \mid X_{-l:-1} = w, X_{1:r} = v)$$

and

$$p(w, a, v) = \mathbb{P}(X_0 = a, X_{-l:-1} = w, X_{1:r} = v),$$

where  $X_{i:j}$  represents the sequence  $X_i, \dots, X_j$ . The operator  $N_n(w, a, v)$  will denote the number of occurrences of the event

$$\{X_{-l:-1} = w\} \cap \{X_0 = a\} \cap \{X_{1:r}\}$$

in the sample. That is

$$N_n(w, a, v) = \sum_{i=1}^n \mathbf{1}\{x_{-l:r}^{(i)} = wav\},$$

where  $wav$  is the concatenation of  $w$ ,  $a$  and  $v$ ; that is  $wav = (w_{-l}, \dots, w_{-1}, a, v_1, \dots, v_r) \in A^{l+r+1}$ . Given  $w$  and  $v$ , the maximum likelihood estimator of the conditional distribution  $\{p(\cdot|w, v) : a \in A\}$  is given by

$$\hat{p}_n(a|w, v) = \frac{N_n(w, a, v)}{N_n(w, v)}, \quad \text{for } a \in A, \quad (2)$$

where  $N_n(w, v) = \sum_{a \in A} N_n(w, a, v)$ . If  $N_n(w, v) = 0$  we adopt the convention  $\hat{p}_n(a|w, v) = 1/|A|$  for all  $a \in A$ .

For any pair of integers  $(l, r)$ , with  $l \leq L_0$  and  $r \leq R_0$  we denote by

$$\hat{\mathbb{P}}_{l,r}(x_0^{(1:n)} | x_{\Delta_{l,r}}^{(1:n)}) = \prod_{w \in A^l} \prod_{v \in A^r} \prod_{a \in A} \hat{p}_n(a|w, v)^{N_n(w, a, v)}. \quad (3)$$

In order to estimate the neighborhood  $\Delta_{l_0, r_0}$ ; that is, to estimate  $l_0$  and  $r_0$ , we propose to use a penalized maximum (conditional) likelihood criterion.

**Definition 2.3.** Given a constant  $c > 0$ , the empirical neighborhood of site 0 is the set of indices  $\Delta_{\hat{l}_n, \hat{r}_n} = \{-\hat{l}_n, \dots, -1, +1, \hat{r}_n\}$ , where

$$(\hat{l}_n, \hat{r}_n) = \arg \max_{0 \leq l \leq L_0, 0 \leq r \leq R_0} \left\{ \log \hat{\mathbb{P}}_{l,r}(x_0^{(1:n)} | x_{\Delta_{l,r}}^{(1:n)}) - c |A|^{l+r} \log_{|A|} n \right\}. \quad (4)$$

We prove the following consistency result for the neighborhood estimator.

**Theorem 2.4.** *The estimator given by (4) satisfies  $(\hat{l}_n, \hat{r}_n) = (l_0, r_0)$  and therefore  $\Delta_{\hat{l}_n, \hat{r}_n}^0 = \Delta_{l_0, r_0}^0$  eventually almost surely as  $n \rightarrow \infty$ .*

The proof of Theorem 2.4 is given in Section 4.

### 3 Variable dependence windows for SNPs maps and disease association

In this paper we model data from 2,062 individuals (72.4% of them females) in which 868 are affected by rheumatoid arthritis (cases) and 1,194 are not affected (controls). This data is the initial batch of whole genome association data for the North American Rheumatoid Arthritis Consortium (NARAC) provided by the Genetic Analysis Workshop 16 (GAW16). For all individuals in this case-control study, information from 545,080 SNP-genotype from the Illumina 550K chip are available. The genotypes are in the format X\_X, where X is a base (A,C,G,T). Each record has information about SNP name, chromosome, and SNP position in basepairs. Only genotypes from the 22 autosomal chromosomes were used in our analysis. For each SNP the scores 0, 1 and 2 were assigned for their three possible SNP genotypes. Thus, for instance, a SNP in which their genotypes are GG, AA, and GA, score 0 was assigned for the homozygote with highest frequency, score 1 for the heterozygote, and score 2 for the homozygote with lowest frequency.

In order to remove potential genotype errors, we excluded those SNPs with minor allele frequency (MAF) lower than 1% as well as those not in Hardy-Weinberg equilibrium (HWE). The HWE was checked by using the Chi-square test available in the genetics library of the R package (R Development Core Team; 2005). The significance level considered was  $10^{-4}$ . At the end, a total of 43,616 SNPs were removed with 501,464 remaining for the analysis. No procedure was used to impute the missing genotypes that remained in the data set.

We apply the model and estimators described in Section 2 to this data set. We obtained in this way neighborhoods for each one of the 501,464 SNPs. Considering the entire data set we obtained neighborhoods with mean 2.22418 SNPs and standard deviation 0.714481 SNP. The mean size of the left part of the neighborhoods was 1.11432 and that of the right part was 1.10985 SNP.

An interesting property of the estimated neighborhoods can be observed in Figure 1,



Figure 1: Left and right neighborhoods for the first 19 SNPs in the sample.

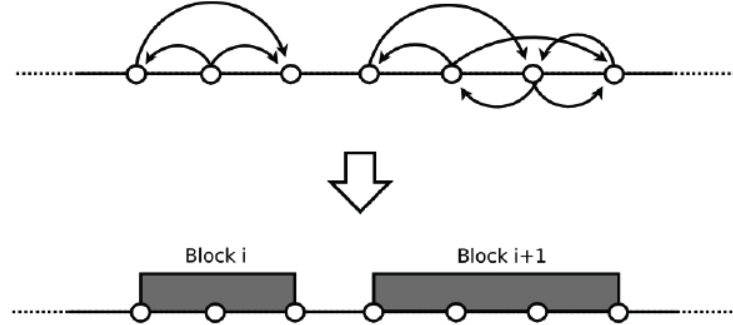


Figure 2: Independent blocks obtained by the identification of intermediate points not included in any neighborhood.

where we represent the length of the left and right parts of each neighborhood by an arrow. In this representation we can see some regions (between two adjacent SNPs) that are not crossed by any arrow; that is by the neighborhoods of the adjacent SNPs. This points divide the set of SNPs into (probabilistically) independent blocks of different sizes (see Remark 2.2). We illustrate how these blocks are obtained in Figure 2. From now on we will call these independent blocks of “influence windows”.

Analyzing the neighborhoods previously determined by the algorithm we obtained a total of 48,697 influence windows. The mean size of these influence windows was 10.27 SNPs, the smallest window has only 1 SNP and the biggest one has 83 SNPs. The standard deviation of the sizes of the influence windows was 5.94 SNPs.

In order to test the association of every influence window with the rheumatoid arthritis, we perform a Chi-square test of independence between the observed genotype frequencies in that window and the response variable indicating the presence/absence of the disease. In Figure 3 we show the scores, corresponding to minus the logarithm in base 10 of the  $p$ -value, calculated for each window in the 22 autosomes. We can observe a region of

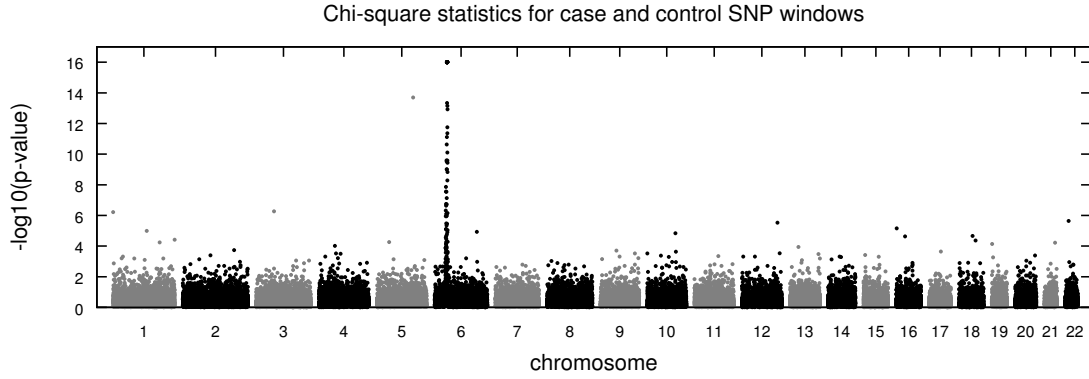


Figure 3: Chi-square statistics for each influence window in the 22 autosomes.

high association in the sixth chromosome, where 22 windows had a  $p$ -value smaller than  $10^{-16}$ . These results are compatible with previous studies about rheumatoid arthritis, as for example Irigoyen et al. (2005); Amos et al. (2009). We can observe also some windows in other chromosomes that exhibited a small  $p$ -value and can therefore be associated with the disease. A list with the influence windows that had a  $p$ -value smaller than  $10^{-4}$ , as well as the program written in C to perform this analysis is available and can be requested from the authors.

## 4 Proof of Theorem 2.4

We begin by giving some basic definitions and stating some results that will be useful in the proof of Theorem 2.4. From now on we simply write  $\log$  for the logarithm in base  $|A|$ .

**Definition 4.1.** The *Kullback-Leibler divergence* between the two probability distributions  $P$  and  $Q$  over  $A$  is defined by

$$D(P; Q) = \sum_{a \in A} P(a) \log \frac{P(a)}{Q(a)}$$

where, by convention,  $P(a) \log \frac{P(a)}{Q(a)} = 0$  if  $P(a) = 0$  and  $P(a) \log \frac{P(a)}{Q(a)} = +\infty$  if  $P(a) > Q(a) = 0$ .



The following lemma was taken from Csiszar and Talata (2006b, Lemma 6.3). We include it here for completeness, but we omit its proof.

**Lemma 4.2.** *For any two probability distributions  $P$  and  $Q$  over  $A$  we have*

$$D(P; Q) \leq \sum_{a \in A: Q(a) > 0} \frac{[P(a) - Q(a)]^2}{Q(a)}.$$

Now we prove a result showing an upper bound for the deviation of the empirical conditional probabilities from their true values.

**Proposition 4.3.** *For any  $\delta > 0$  and for any triple  $(w, a, v) \in A^{l+r+1}$  with  $0 \leq l \leq L_0$  and  $0 \leq r \leq R_0$  we have*

$$|\hat{p}_n(a|w, v) - p(a|w, v)| < \sqrt{\frac{\delta \log n}{N_n(w, v)}}$$

eventually almost surely as  $n \rightarrow \infty$ .

*Proof.* Define, for fixed  $(w, a, v) \in A^{l+r+1}$ , the random variables

$$Y_i = \mathbf{1}\{x_{-l:r}^{(i)} = wav\} - p(a|w, v)\mathbf{1}\{x_{-l:-1}^{(i)} = w\}\mathbf{1}\{x_{1:r}^{(i)} = v\}, \quad i = 1, 2, \dots, n$$

and

$$Z_n = \sum_{i=1}^n Y_i = N_n(w, a, v) - p(a|w, v)N_n(w, v). \quad (5)$$

The variables  $\{Y_i: i = 1, 2, \dots, n\}$  are i.i.d and a direct calculation gives, for any  $i = 1, \dots, n$ ,  $\mathbb{E}(Y_i) = 0$  and

$$\mathbb{E}(Y_i^2) = p(a|w, v)(1 - p(a|w, v))p(w, v) \leq \frac{p(w, v)}{4},$$

where  $p(w, v) = \sum_{a' \in A} p(w, a', v)$ . Now, by the Law of the Iterated Logarithm we have

that for any  $\epsilon > 0$

$$|Z_n| < (1 + \epsilon) \frac{p(w, v)}{4} \sqrt{2n \log \log n}$$

eventually almost surely as  $n \rightarrow \infty$ . In particular we have

$$|Z_n| < \sqrt{2p(w, v)^2 n \log \log n}$$

eventually almost surely as  $n \rightarrow \infty$ . Dividing both sides of the inequality by  $N_n(w, v)$  we obtain that

$$|\hat{p}_n(a|w, v) - p(a|w, v)| < \sqrt{\frac{2p(w, v)^2 n \log \log n}{N_n(w, v)^2}}.$$

By the Strong Law of Large Numbers we have that  $n/N_n(w, v) \rightarrow 1/p(w, v)$  almost surely, therefore we have

$$|\hat{p}_n(a|w, v) - p(a|w, v)| < \sqrt{\frac{4p(w, v) \log \log n}{N_n(w, v)}}$$

eventually almost surely as  $n \rightarrow \infty$ . Now, for any  $\delta > 0$  we have that

$$4p(w, v) \log \log n < \delta \log n$$

eventually as  $n \rightarrow \infty$ , and this concludes the proof of Proposition 4.3 . □

*Proof of Theorem 2.4.* Denote by

$$\text{PML}_{l,r}(x_0^{(1:n)} | x_{\Delta_{l,r}}^{(1:n)}) = \log \hat{\mathbb{P}}_{l,r}(x_0^{(1:n)} | x_{\Delta_{l,r}}^{(1:n)}) - c|A|^{l+r} \log n.$$

We will divide the proof in two cases.

(a) *Overestimation.* We have to prove that simultaneously for all pairs  $(l, r) \neq (l_0, r_0)$ , with  $l_0 \leq l \leq L_0, r_0 \leq r \leq R_0$  we will have

$$\text{PML}_{l,r}(x_0^{(1:n)} | x_{\Delta_{l,r}}^{(1:n)}) < \text{PML}_{l_0,r_0}(x_0^{(1:n)} | x_{\Delta_{l_0,r_0}}^{(1:n)})$$

eventually almost surely as  $n \rightarrow \infty$ .

Observe that

$$\begin{aligned} \text{PML}_{l_0, r_0}(x_0^{(1:n)} | x_{\Delta_{l_0, r_0}}^{(1:n)}) - \text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)}) = \\ c(|A|^{l+r} - |A|^{l_0+r_0}) \log n - \sum_{wav \in A^{l+r+1}} N(wav) \log \frac{\hat{p}(a|w, v)}{\hat{p}(a|w_{-l_0:-1}, v_{1:r_0})}, \end{aligned} \quad (6)$$

where by an abuse of notation we write  $N(wav) = N_n(w, a, v)$  and  $\hat{p}(a|w, v) = \hat{p}_n(a|w, v)$ .

As these empirical probabilities are the maximum likelihood estimators we have that

$$\begin{aligned} \sum_{wav \in A^{l+r+1}} N(wav) \log \hat{p}(a|w_{-l_0:-1}, v_{1:r_0}) &\geq \sum_{wav \in A^{l+r+1}} N(wav) p(a|w_{-l_0:-1}, v_{1:r_0}) \\ &= \sum_{wav \in A^{l+r+1}} N(wav) p(a|w, v). \end{aligned}$$

Therefore, (6) can be upper-bounded by

$$c \left(1 - \frac{1}{|A|}\right) |A|^{l+r} \log n - \sum_{wav \in A^{l+r+1}} N(wav) \log \frac{\hat{p}(a|w, v)}{p(a|w, v)}.$$

Now observe that

$$\sum_{wav \in A^{l+r+1}} N(wav) \log \frac{\hat{p}(a|w, v)}{p(a|w, v)} = \sum_{w \cdot v \in A^{l+r}} N(w \cdot v) D(\hat{p}(\cdot|w, v); p(\cdot|w, v)),$$

where  $D$  denotes the *Kullback-Leibler divergence* (see Definition 4.1 in the the Appendix).

Therefore, by Lemma 4.2 and Proposition 4.3 we have that for any  $\delta > 0$

$$\begin{aligned}
& \sum_{w \cdot v \in A^{l+r}} N(w \cdot v) D(\hat{p}(\cdot|w, v); p(\cdot|w, v)) \\
& \leq \sum_{w \cdot v \in A^{l+r}} N(w \cdot v) \sum_{a \in A} \frac{[\hat{p}(a|w, v) - p(a|w, v)]^2}{p(a|w, v)} \\
& \leq \sum_{w \cdot v \in A^{l+r}} N(w \cdot v) \sum_{a \in A} \frac{\delta \log n}{N(w \cdot v) p(a|w, v)} \\
& \leq \frac{\delta |A|^{l+r+1} \log n}{p_{\min}},
\end{aligned}$$

eventually almost surely as  $n \rightarrow \infty$ , where

$$p_{\min} = \min\{p(a|w, v) : p(a|w, v) > 0, a \in A, w \in A^{l_0}, v \in A^{r_0}\}.$$

Then if we take  $\delta < c p_{\min}(|A| - 1)/|A|^2$  we have that eventually almost surely as  $n \rightarrow \infty$

$$\text{PML}_{l_0, r_0}(x_0^{(1:n)} | x_{\Delta_{l_0, r_0}}^{(1:n)}) > \text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)})$$

simultaneously for all pairs  $(l, r) \neq (l_0, r_0)$ , with  $l_0 \leq l \leq L_0$ ,  $r_0 \leq r \leq R_0$ . This completes the proof of part (a).

(b) *Underestimation.* We have to prove that simultaneously for all pairs  $(l, r)$  with  $l < l_0$  or  $r < r_0$  we have

$$\text{PML}_{l_0, r_0}(x_0^{(1:n)} | x_{\Delta_{l_0, r_0}}^{(1:n)}) > \text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)})$$

eventually almost surely as  $n \rightarrow \infty$ .

First consider the case  $l \leq l_0$  and  $r \leq r_0$ . In this case we have that

$$\begin{aligned} \text{PML}_{l_0, r_0}(x_0^{(1:n)} | x_{\Delta_{l_0, r_0}}^{(1:n)}) - \text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)}) &= \\ &= \sum_{wav \in A^{l_0+r_0+1}} N(wav) \log \frac{\hat{p}(a|w, v)}{\hat{p}(a|w_{-l:-1}, v_{1:r})} - c(|A|^{l_0+r_0} - |A|^{l+r}) \log n \\ &= n \left[ \sum_{wav \in A^{l_0+r_0+1}} \frac{N(wav)}{n} \log \frac{\hat{p}(a|w, v)}{\hat{p}(a|w_{-l:-1}, v_{1:r})} - c(|A|^{l_0+r_0} - |A|^{l+r}) \frac{\log n}{n} \right]. \end{aligned}$$

By the Strong Law of Large Numbers we have that

$$\begin{aligned} \sum_{wav \in A^{l_0+r_0+1}} \frac{N(wav)}{n} \log \frac{\hat{p}(a|w, v)}{\hat{p}(a|w_{-l:-1}, v_{1:r})} \\ \longrightarrow \sum_{wav \in A^{l_0+r_0+1}} p(wav) \log \frac{p(a|w, v)}{p(a|w_{-l:-1}, v_{1:r})} \end{aligned}$$

almost surely as  $n \rightarrow \infty$ , where  $p(wav) = \mathbb{P}(X_0 = a, X_{\Delta_{l_0, r_0}} = wav)$ . The Log-Sum inequality and the minimality of  $(l_0, r_0)$  (see Remark 2.1) implies that

$$\sum_{wav \in A^{l_0+r_0+1}} p(wav) \log \frac{p(a|wv)}{p(a|w_{-l:-1}, v_{1:r})} > 0$$

As the number of pairs  $(l, r) \neq (l_0, r_0)$  satisfying  $l \leq l_0$  and  $r \leq r_0$  is finite, this implies that simultaneously for all such pairs we will have

$$\text{PML}_{l_0, r_0}(x_0^{(1:n)} | x_{\Delta_{l_0, r_0}}^{(1:n)}) > \text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)})$$

eventually almost surely as  $n \rightarrow \infty$ .

Now consider the case  $(l, r)$  with  $l_0 < l \leq L_0$  and  $r < r_0$ . We will prove that simultaneously for all  $l_0 < l \leq L_0$ ,

$$\text{PML}_{l, r}(x_0^{(1:n)} | x_{\Delta_{l, r}}^{(1:n)}) < \text{PML}_{l_0, r}(x_0^{(1:n)} | x_{\Delta_{l_0, r}}^{(1:n)})$$

eventually almost surely as  $n \rightarrow \infty$ . The proof of this fact follows the same arguments of part (a), by observing that

$$\begin{aligned}
\text{PML}_{l_0,r}(x_0^{(1:n)}|x_{\Delta_{l_0,r}}^{(1:n)}) - \text{PML}_{l,r}(x_0^{(1:n)}|x_{\Delta_{l,r}}^{(1:n)}) &\geq c \left(1 - \frac{1}{|A|}\right) |A|^{l+r} \log n \\
&\quad - \sum_{wv \in A^{l+r+1}} N(wav) \log \frac{\hat{p}(a|w,v)}{p(a|w,v)} \\
&\geq \left[ c \left(1 - \frac{1}{|A|}\right) - \frac{\delta |A|}{p_{\min}} \right] |A|^{l+r} \log n \\
&> 0
\end{aligned}$$

by Proposition 4.3, for a sufficiently small  $\delta$ , eventually almost surely as  $n \rightarrow \infty$  and simultaneously for all  $l_0 < l \leq L_0$ . This fact, combined with what was proved for the pair  $(l_0, r)$  before implies that

$$\text{PML}_{l,r}(x_0^{(1:n)}|x_{\Delta_{l,r}}^{(1:n)}) < \text{PML}_{l_0,r_0}(x_0^{(1:n)}|x_{\Delta_{l_0,r_0}}^{(1:n)})$$

eventually almost surely as  $n \rightarrow \infty$ , simultaneously for all  $r < r_0$  and  $l_0 \leq l \leq L_0$ .

By observing that the same proof applies to the case  $(l, r)$  with  $l < l_0$  and  $r_0 < r \leq R_0$ , this finishes the proof of part (b).

□

## Discussion

In this paper we presented a method based on the theory of variable range Markov random fields to estimate the extent of dependence among SNPs allowing variable windows along the genome. We proposed an estimator based on the idea of penalized maximum likelihood to find the conditional dependence neighborhood of each SNP in the sample and we proved its consistency. A major advantage of our method is that it is adaptive for the extent of dependencies among SNPs and it is not necessary to specify a window size to capture the

dependency pattern which is a problem in most sliding-windows approaches.

The core of our method is to find the basic neighborhoods of long sequences of SNPs, without taking into account the disease status, and then to test the association of each independent block with the disease. Therefore, the method can be used for association with many different types of trait data, such as quantitative traits. It could also be applied to other platform types, like multiallelic markers (e.g. microsatellites), as well as to other data sequences, like nucleotide or aminoacid sequences. In our analysis we considered genotypic data sequences, on the level of individuals, but another option is to use haplotype data, on the level of chromosomes, by phasing allele data. The challenge in the latter is to estimate the phase of the data, but good haplotype-phasing computer programs are now available. The flexibility of our method to handle genotype or haplotype data may be useful to assess different disease models.

A reasonably large sample size is required to attain consistency of our neighborhood estimator. Rare long SNPs blocks, which may be present in the population, are expected to be observed in low frequency and may bias the findings. In this direction, an open question is how to obtain lower bounds for the sample size to guarantee a given level of precision for the neighborhood estimator. Beyond the sample size, the results are dependent of the density of the SNPs covering the genome and also of the size of the alphabet being modeled. For biallelic markers, as SNPs, these problems become less severe.

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